

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 September 2005 (09.09.2005)

PCT

(10) International Publication Number
WO 2005/083118 A3

(51) International Patent Classification:
C12Q 1/68 (2006.01)

(21) International Application Number:
PCT/JP2005/002090

(22) International Filing Date: 4 February 2005 (04.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/548,335 27 February 2004 (27.02.2004) US

(71) Applicants (for all designated States except US): **ONCOTHERAPY SCIENCE, INC.** [JP/JP]; 2-1, Sakado 3-chome, Takatsu-ku, Kawasaki-shi, Kanagawa 2130012 (JP). **THE UNIVERSITY OF TOKYO** [JP/JP]; 3-1, Hongo 7-chome, Bunkyo-ku, Tokyo 1138654 (JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **NAKAMURA, Yusuke** [JP/JP]; 17-33, Azamino 1-chome, Aoba-ku, Yokohama-shi, Kanagawa 2250011 (JP). **NAKAGAWA, Hidewaki** [JP/JP]; 36-11-103, Kamiosaki 3-chome, Shinagawa-ku, Tokyo 1410021 (JP). **NAKATSURU, Shuichi** [JP/JP]; 6-2, Shimoochiai 2-chome, Chuo-ku, Saitama-shi, Saitama 3380002 (JP).

(74) Agents: **SHIMIZU, Hatsushi** et al.; Kantetsu Tsukuba Bldg. 6F., 1-1-1, Oroshi-machi, Tsuchiura-shi, Ibaraki 3000847 (JP).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

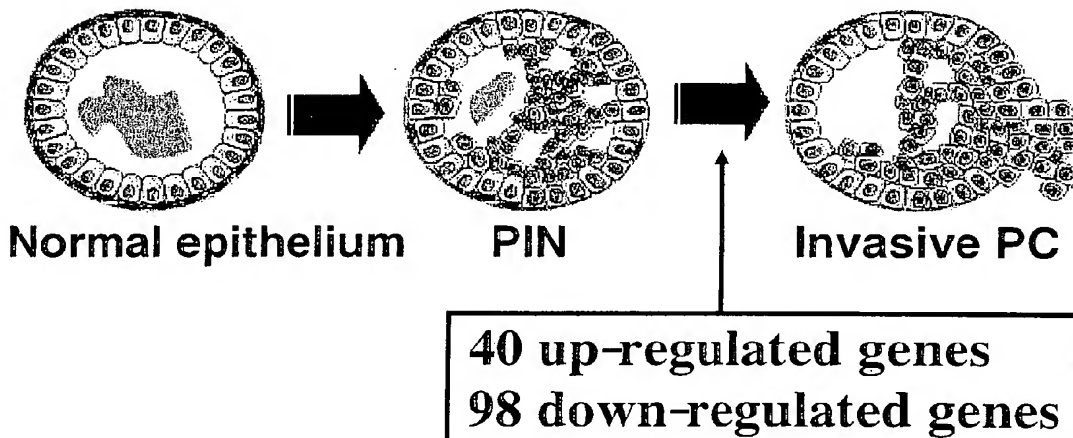
Published:

— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
13 April 2006

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PIN-PRC TRANSITION GENES



(57) Abstract: Objective methods for diagnosing a predisposition to developing prostate cancer (PRC) are described herein. In one embodiment, the diagnostic method involves the determining a expression level of PRC -associated gene that discriminate between PRC and PIN. The present invention further provides methods of screening for therapeutic agents useful in the treatment of PRC, methods of treating PRC.

WO 2005/083118 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2005/002090

A. CLASSIFICATION OF SUBJECT MATTER

C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, Sequence Search, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ASHIDA SHINGO ET AL: "Molecular features of the transition from prostatic intraepithelial neoplasia (PIN) to prostate cancer: Genome-wide gene-expression profiles of prostate cancers and PINs" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 64, no. 17, 1 September 2004 (2004-09-01), pages 5963-5972, XP002339625 ISSN: 0008-5472 table 3 ----- -/--	1-3, 6-12, 16-26, 30, 31



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

17 October 2005

Date of mailing of the international search report

28. 02. 2006

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Guarinos Viñals, E

INTERNATIONAL SEARCH REPORT

ational Application No

ru/JP2005/002090

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>LI Y ET AL: "Gene expression profiling clearly separates hyperplasia from PIN and PIN from prostate carcinoma a microdissection and microarray study" PATHOLOGY RESEARCH AND PRACTICE, vol. 200, no. 4, 2004, page 302, XP002349447</p> <p>& 88TH MEETING OF THE GERMAN SOCIETY OF PATHOLOGY; ROSTOCK, GERMANY; JUNE 02-05, 2004</p> <p>ISSN: 0344-0338</p> <p>the whole document</p> <p>-----</p>	<p>1-3, 6-12, 16-26, 30,31</p>
P,X	<p>WO 2004/031414 A (ONCOTHERAPY SCIENCE, INC; JAPAN AS REPRESENTED BY THE PRESIDENT OF THE) 15 April 2004 (2004-04-15)</p> <p>page 51; table 5; sequence PRC296</p> <p>page 66; table 2; sequences 7, 8</p> <p>-----</p>	<p>1-3, 6-12, 16-26, 30,31</p>
P,X	<p>WO 2004/058051 A (THE INSTITUTE FOR SYSTEMS BIOLOGY; AEBERSOLD, RUDOLF, H; WRIGHT, MICHA) 15 July 2004 (2004-07-15)</p> <p>page 68, line 41</p> <p>-----</p>	<p>1-3, 6-12, 16-26, 30,31</p>
X	<p>WO 03/060148 A (THE INSTITUTE FOR SYSTEMS BIOLOGY; LIN, BIAOYANG)</p> <p>24 July 2003 (2003-07-24)</p> <p>page 119 - page 120; example II</p> <p>-----</p>	<p>1-3, 6-12, 16-26, 30,31</p>
X	<p>"Affymetrix GeneChip Human Genome U133 Array Set HG-U133A"</p> <p>GENBANK GEO, 11 March 2002 (2002-03-11), XP002349448</p> <p>the whole document</p> <p>-----</p>	<p>21,22</p>
X	<p>WO 03/070889 A (IDEC PHARMACEUTICALS CORPORATION; GATELY, DENNIS)</p> <p>28 August 2003 (2003-08-28)</p> <p>paragraph '0291!</p> <p>-----</p>	<p>1-3, 6-12, 16-26, 30,31</p>
X	<p>US 2003/190640 A1 (FARIS MARY 'US! ET AL)</p> <p>9 October 2003 (2003-10-09)</p> <p>page 18; table 1; sequence 58</p> <p>-----</p>	<p>1-3, 6-12, 16-26, 30,31</p>
X	<p>US 2003/219760 A1 (GORDON GAVIN J ET AL)</p> <p>27 November 2003 (2003-11-27)</p> <p>table 11</p> <p>-----</p>	<p>1-3, 6-12, 16-26, 30,31</p>
-/--		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP2005/002090

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/31209 A (THE GOVERNMENT OF UNITED STATES OF AMERICA, AS REPRESENTED BY THE SECR) 18 April 2002 (2002-04-18) page 92; table 1	1-3, 6-12, 16-26, 30, 31
A	----- TENNANT MARIE K ET AL: "Insulin-like growth factor-binding protein-2 and -3 expression in benign human prostate epithelium, prostate intraepithelial neoplasia, and adenocarcinoma of the prostate" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, NEW YORK, NY, US, vol. 81, no. 1, 1996, pages 411-420, XP002266907 ISSN: 0021-972X figure 8	
A	----- YING SHAO-YAO ET AL: "Gene expression in precursor cells of prostate cancer associated with activin by combination of subtractive hybridization and microarray technologies." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 313, no. 1, 2 January 2004 (2004-01-02), pages 104-109, XP002349449 ISSN: 0006-291X -----	

INTERNATIONAL SEARCH REPORT

national application No.
PCT/JP2005/002090

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13, 14, 28, 32
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 16-20, as far as an "in vivo" method is concerned, and claims 23-26, 29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 28, 32
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 6-14, 16-26, 28, 30-32 partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Continuation of Box II.1

Although claims 16-20, as far as an "in vivo" method is concerned, and claims 23-26, 29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: 13, 14, 28, 32

Claims 13 and 14 relate to a prostate cancer (PRC) reference expression profile that comprises the expression pattern of two or more genes selected from the group consisting of PRC 1-138 or PRC 1-40. An expression profile is defined in page 7, lines 11-14 of the present application as the level of expression of these genes. The subject-matter of claims 13 and 14 is a mere presentation of information for which no search is required as specified in Rule 39.1(v) PCT. No search was therefore carried out by the International Searching Authority on the subject-matter of claims 13 and 14.

Continuation of Box II.2

Claims Nos.: 28, 32

Present claims 28 and 32 relate to a product defined by reference to a desirable characteristic or property, namely its capacity of being identified by a screening method. The claims cover all products having this characteristic or property, whereas the application provides no support within the meaning of Article 6 PCT and no disclosure within the meaning of Article 5 PCT for any of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for the subject-matter of claims 28 and 32.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is

normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1-3, 6-14, 16-26, 28, 30-32 partially

Invention 1: a method for diagnosing a predisposition to developing prostate cancer by determining the level of expression of PRC1 (ABHD2), a PRC reference expression profile comprising a pattern of expression of PRC1, a method of screening for a compound that binds to the PRC1 polypeptide, a kit comprising a detection reagent which binds to PRC1, an array comprising a nucleic acid which binds to PRC1, a method of treating or preventing prostate cancer by administering an antisense of PRC1, a method of treating or preventing prostate cancer by administering an siRNA against PRC1, a method of treating or preventing prostate cancer by administering an antibody that binds PRC1, a method of treating or preventing prostate cancer by administering a PRC1 polypeptide, a composition comprising an antisense of PRC1 and a composition comprising an antibody that binds PRC1.

Invention 2: the same as Invention 1 but concerning PRC2.

Invention 3: the same as Invention 1 but concerning PRC3.

Invention 4: the same as Invention 1 but concerning PRC4.

.....

Invention 40: the same as Invention 1 but concerning PRC40.

Invention 41: claims 1, 4-13, 15-22, 27-29, 32 partially

Invention 41: a method for diagnosing a predisposition to developing prostate cancer by determining the level of expression of PRC41, a PRC reference expression profile comprising a pattern of expression of PRC41, a method of screening for a compound that binds to the PRC41 polypeptide, a kit comprising a detection reagent which binds to PRC41, an array comprising a nucleic acid which binds to PRC41, a method of treating prostate cancer by administering a compound that increases the expression or activity of PRC41 and a method of treating prostate cancer by administering the PRC41 polypeptide.

Invention 42: the same as Invention 41 but concerning PRC42.

Invention 43: the same as Invention 41 but concerning PRC43.

Invention 44: the same as Invention 41 but concerning PRC44.

.....

Invention 138: the same as Invention 41 but concerning PRC138.

INTERNATIONAL SEARCH REPORT

Information on patent family members

ational Application No

PCT/JP2005/002090

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004031414	A	15-04-2004	AU 2003263611 A1	23-04-2004
			AU 2003264881 A1	23-04-2004
			CA 2500859 A1	15-04-2004
			CA 2500861 A1	15-04-2004
			CN 1701078 A	23-11-2005
			CN 1703523 A	30-11-2005
			EP 1546411 A2	29-06-2005
			EP 1546197 A2	29-06-2005
			WO 2004031231 A2	15-04-2004
			JP 2006500950 T	12-01-2006
WO 2004058051	A	15-07-2004	AU 2003303379 A1	22-07-2004
			US 2004121413 A1	24-06-2004
WO 03060148	A	24-07-2003	AU 2003205194 A1	30-07-2003
			CA 2474151 A1	24-07-2003
			EP 1573031 A2	14-09-2005
			JP 2005527196 T	15-09-2005
			US 2003144188 A1	31-07-2003
WO 03070889	A	28-08-2003	AU 2003217421 A1	09-09-2003
US 2003190640	A1	09-10-2003	NONE	
US 2003219760	A1	27-11-2003	NONE	
WO 0231209	A	18-04-2002	AU 1457602 A	22-04-2002